Bidirectional relationship between chronic kidney and periodontal disease: a study using structural equation modeling

Monica A. Fisher[1], George W. Taylor[2], Brady T. West[3] and Ellen T. McCarthy[4]

[1]Department of Preventive Medicine and Public Health, University of Kansas School of Medicine, Wichita, Kansas, USA; [2]Department of Cariology, Restorative Sciences and Endodontics, University of Michigan School of Dentistry and School of Public Health, Ann Arbor, Michigan, USA; [3]Survey Research Center, Institute for Social Research, University of Michigan, Ann Arbor, Michigan, USA and [4]Kidney Institute, University of Kansas Medical Center, Kansas City, Kansas, USA

Periodontal disease is associated with diabetes, heart disease, and chronic kidney disease (CKD), relationships postulated to be due in part to vascular inflammation. A bidirectional relationship between CKD and periodontal disease is plausible, though this relationship has not been previously reported. In this study, we assessed the potential for connections between CKD and periodontal disease, and mediators of these relationships using structural equation models of data from 11,211 adults ⩾18 years of age who participated in the Third National Health and Nutrition Examination Survey. Multivariable logistic regression models were used to test the hypothesis that periodontal disease was independently associated with CKD. Given the potential that the periodontal disease and CKD relationship may be bidirectional, a two-step analytic approach was used that involved tests for mediation and structural equation models to examine more complex direct and indirect effects of periodontal disease on CKD, and vice versa. In two separate models, periodontal disease (adjusted odds ratio of 1.62), edentulism (adjusted odds ratio of 1.83), and the periodontal disease score were associated with CKD when simultaneously adjusting for 14 other factors. Altogether, three of four structural equation models support the hypothesized relationship. Thus, our analyses support a bidirectional relationship between CKD and periodontal disease, mediated by hypertension and the duration of diabetes.

Kidney International (2011) **79,** 347–355; doi:10.1038/ki.2010.384; published online 6 October 2010

KEYWORDS: chronic inflammation; chronic kidney disease; diabetes mellitus; hypertension; statistics

Correspondence: *Monica A. Fisher, Department of Preventive Medicine and Public Health, University of Kansas School of Medicine, 1010 N. Kansas Street, Suite 1406, Wichita, Kansas 67214-3199, USA. E-mail: mfisher2@kumc.edu*

Received 15 December 2009; revised 12 July 2010; accepted 3 August 2010; published online 6 October 2010

Increasing prevalence of chronic kidney disease (CKD) is an important public health problem, especially in older adults. The number of Americans with CKD continues to increase with more than 20 million adults affected, many of whom are undiagnosed.[1–3] The burden of CKD in terms of medical costs and shortened healthy life is onerous, and individuals with CKD have markedly increased risk of end-stage renal disease, cardiovascular disease, and premature death.[4–6]

Multivariable regression models have been developed recently to aid in the early identification of patients at high risk for CKD. These models include the following factors: older age, race/ethnicity, gender, education, lower income, periodontal status, smoking status, diabetes and poor glycemic control, hypertension, anemia, cardiovascular disease, congestive heart failure, peripheral vascular disease, macroalbuminuria, high total cholesterol, low high-density lipoprotein, high C-reactive protein (CRP), body mass index (BMI), annual physician visit, and hospitalisations in the past year.[7–10]

An increasing body of epidemiologic evidence supports an association between periodontal disease and CKD.[7–11] Periodontal disease was associated with a fivefold increased risk of cardiovascular disease-related death in a retrospective study of hemodialysis patients, after simultaneously taking into account other important correlates of CKD.[12]

Periodontal disease is a chronic infection accompanied by a systemic inflammatory response that may add to the chronic inflammation present in CKD.[13–15] Thus, in addition to leading to tooth loss and being a major cause of edentulism,[16] periodontal disease may contribute to CKD. The systemic inflammatory response seen in periodontal disease has several components, including dissemination of periodontal pathogenic bacteria and their products,[17,18] as well as locally produced inflammatory mediators. Furthermore, elevated levels of the acute-phase reactant CRP are associated with periodontal disease and edentulism.[19,20] Molecular and cellular mechanisms have been suggested through studies of periodontal clinical status, infectious burden, and host responses to periodontal pathogens.[21–22]

The objective of the study was to assess the potential bidirectional relationship between CKD and periodontal disease, and potential mediators of this relationship using structural equation models. By fitting structural equation models the authors investigated whether hypothetical causal structures between CKD, diabetes, hypertension, and periodontal disease are statistically plausible.

RESULTS

Multivariable logistic regression modeling

Multivariable logistic regression models are used to evaluate the direct effect of one factor (periodontal disease) on the outcome (CKD) while simultaneously controlling for direct effects of many other factors (diabetes, hypertension, socioeconomic status, and so on) in Table 1. Model 1 was developed by expanding a previously reported model[9] to include 15 potential risk factors including diabetes status, BMI, and CRP. In the simpler model 2, a previously reported approach[23] assessed the role of diabetes in CKD by taking into account 6 of the 15 variables included in model 1. Model 3 reports the independent association of 12 of the 15 variables in model 1, along with the continuous measure of diabetes duration and excluding periodontal disease. Lastly, model 4 consists of model 3 plus periodontal disease score to determine the independent association between periodontal disease score and CKD, and to depict the impact of periodontal disease score on the other 14 potential risk factors.

Periodontal status was independently associated with CKD in models 1 and 4 after simultaneously taking into account all other factors as listed in Table 1. In model 1, edentulous adults and adults with periodontal disease were approximately twice as likely to have CKD (adjusted odds ratio (OR_{Adj}) = 1.83; confidence intervals 95% (95% CIs): 1.31–2.55 and OR_{Adj} = 1.62; 95% CI: 1.17–2.26, respectively), after adjusting for 14 other potential risk factors. Diabetes status was not significant in model 1 and addition of diabetes status, BMI, and CRP to the previously published model of CKD[9] led to an average 2.36% change in the effect of the other potential risk factors. Unexpectedly, diabetes glycemic control was not significant when 14 other potential risk factors were simultaneously considered. However, when only 6 of the 15 variables were considered in model 2, adults with poor glycemic control were almost twice as likely to have CKD than those without diabetes (OR_{Adj} = 1.74; 95% CI: 1.02–2.97), after adjusting for age, race/ethnicity, gender, hypertension, and BMI. Not surprisingly, in model 3, diabetes duration was independently associated with CKD when periodontal disease was excluded as one of 14 potential risk factors (OR_{Adj} = 1.02; 95% CI: 1.00–1.05). In model 4, periodontal disease score was statistically significant, such that for every 1-unit increase in the continuous periodontal disease score, the odds of having CKD are 1.01 times greater, or increased by 1%, when adjusting for the other factors.

In summary, we used logistic regression analyses to test the hypothesis that periodontal disease is independently associated with CKD in two separate models (models 1 and 4). We found edentulous adults and adults with periodontal disease were more likely to have CKD than those without periodontal disease, after simultaneously adjusted for 14 other potential risk factors, including glycemic control in model 1 and diabetes duration in model 4.

Examination of diabetes and hypertension as possible mediators of the relationship between CKD and periodontal disease

In the linear regression model for duration of diabetes (continuous) as a function of periodontal disease and the other potential risk factors (hypertension, age, race/ethnicity, gender, income, macroalbuminuria, cholesterol, high-density lipoprotein, smoking, hospitalisation in the past year, and physician visit in the past year), periodontal disease was significantly associated with diabetes duration. Adults with periodontal disease or who were edentulous had significantly higher mean diabetes duration, relative to adults without periodontal disease. Given the significant relationship of periodontal disease and CKD when not including diabetes status in the model,[9] a second model was fitted adding diabetes duration as a potential risk factor of CKD that found the relationship of diabetes duration with CKD was significant, and the relationship of periodontal disease with CKD remained significant and was unchanged when diabetes duration was included in the model.

Hypertension was also found to be a mediator of the relationship between periodontal disease and CKD through diabetes. Periodontal disease was significantly associated with hypertension when controlling for diabetes duration (continuous). In other words, adults with periodontal disease or who were edentulous were significantly more likely to have hypertension than adults without periodontal disease when controlling for the other factors, including diabetes duration. When hypertension was added to an initial model of CKD (previous study[9] only excluding hypertension) along with periodontal disease, the relationship of periodontal disease with CKD remained significant and was slightly attenuated. The relationship of hypertension with CKD was also significant, suggesting partial mediation of the periodontal disease and CKD relationship. Collectively, these analyses provide initial empirical support for possible mediation of the periodontal disease and CKD relationship by hypertension.

Structural equation models

An additional table depicting findings is available as Supplementary Information at http://www.nature.com/ki.

Use of structural equation modeling adds important insight to the relationship between periodontal disease and CKD because it allows us to examine more complex direct and indirect effects of periodontal disease on CKD and vice versa. As with the multiple logistic regression models described above, we designed several different structural equation models to assess the possible bi-directional relationship between periodontal disease and CKD.

Table 1 | Multivariable logistic regression models of the association with chronic kidney disease[a]

Explanatory variables	Model 1 OR_{Adj} (95% CI)	Model 2 (ref. 23) OR_{Adj} (95% CI)	Model 3 OR_{Adj} (95% CI)	Model 4 OR_{Adj} (95% CI)
Periodontal status				
Edentulous	1.83 (1.31–2.55)*			
Periodontal disease	1.62 (1.17–2.26)*			
Periodontal disease score[b]				1.01 (1.01–1.02)*
60+ Year olds	10.05 (6.77–14.92)*	15.62 (10.37–23.52)*	11.65 (7.79–17.42)*	8.70 (5.70–13.28)*
Macroalbuminuria	5.53 (2.97–10.32)*		5.33 (2.86–9.94)*	4.96 (2.63–9.38)*
Race/ethnicity				
Non-Hispanic white	3.45 (2.31–5.14)*	3.07 (2.17–4.36)*	3.82 (2.62–5.56)*	3.46 (2.34–5.10)*
Non-Hispanic black	2.26 (1.46–3.50)*	2.20 (1.43–3.38)*	2.67 (1.72–4.14)*	2.40 (1.53–3.78)*
Hypertension	2.18 (1.69–2.82)*	2.49 (1.96–3.18)*	2.33 (1.75–3.12)*	2.19 (1.64–2.94)*
Smoking status				
Former smoker	1.96 (1.38–2.80)*		2.24 (1.37–3.67)*	2.31 (1.41–3.79)*
Never smoker	1.58 (1.13–2.22)*		1.62 (1.01–2.61)*	1.86 (1.14–3.03)*
Low HDL	1.81 (1.21–2.69)*		1.84 (1.19–2.84)*	1.74 (1.13–2.70)*
Hospitalized in past year	1.62 (1.18–2.23)*		1.73 (1.29–2.32)*	1.66 (1.22–2.25)*
Low income	1.63 (1.28–2.07)*		1.83 (1.46–2.30)*	1.51 (1.15–1.99)*
Annual physician visit	1.65 (1.08–2.53)*		1.64 (1.02–2.65)*	1.68 (1.03–2.73)*
High cholesterol	1.50 (1.16–1.96)*		1.61 (1.23–2.10)*	1.57 (1.21–2.03)*
Female	1.43 (1.03–1.99)*	1.32 (1.00–1.74)*	1.41 (0.97–2.03)	1.35 (0.93–1.98)
Diabetes status				
Poor control	0.98 (0.67–1.43)	1.74 (1.02–2.97)*		
Better control	0.91 (0.51–1.64)	1.09 (0.78–1.54)		
Diabetes duration[c]			1.02 (1.00–1.05)*	1.02 (1.00–1.04)
Body mass index (kg/m^2)	0.99 (0.97–1.01)	1.00 (0.98–1.03)	0.99 (0.96–1.02)	0.99 (0.96–1.02)
C-reactive protein (mg/dl)	1.15 (1.01–1.32)*		1.16 (1.02–1.32)*	1.13 (1.00–1.28)

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; HDL, high-density lipoprotein; OR_{Adj}, adjusted odds ratio for the association between chronic kidney disease, simultaneously taking into account all the listed factors.
[a]Excluded those who report never or former smoking with serum cotinine level indicating current smoker.
[b]For every 1-unit increase in the continuous periodontal disease score, the odds of having CKD are 1.01 times greater, or increased by 1%, when adjusting for the other factors.
[c]For every 1-year increase in diabetes duration, the odds of having CKD are 1.02 times greater, or increased by 2%, when adjusting for the other factors.
*$P < 0.05$.

Models A and B depict the structural equation models for the outcome CKD. When assessing the role of periodontal disease leading to diabetes in model A, periodontal disease has a significant direct effect on CKD, and has this effect indirectly through diabetes duration and hypertension. In other words, periodontal disease has a significant direct effect on diabetes duration; diabetes duration has a significant direct effect on hypertension, and hypertension had a significant direct effect on CKD. These results suggest that the individuals with increased periodontal disease score were more likely to have CKD when taking the other relationships in this model into account. These results also suggest that diabetes duration has an effect on CKD indirectly through hypertension, but unexpectedly does not directly impact CKD. Using the MPlus analysis to measure fit, this model has a close fit, which indicates this pathway is statistically plausible. Next, when assessing the role of diabetes leading to periodontal disease in model B, this model also has an acceptable fit and provides additional support for a significant direct effect of periodontal disease on CKD, and provides further evidence of significant indirect effects of diabetes duration on CKD operating through periodontal disease and hypertension.

Models C and D depict the structural equation models for the outcome periodontal disease. When assessing the role of periodontal disease leading to diabetes in model C, CKD has a significant direct effect on periodontal disease score, whereas diabetes duration has a significant indirect effect on periodontal disease through hypertension and CKD. These results suggest that increased periodontal disease score is associated with increased duration of diabetes, which in turn leads to increased probability of hypertension, which in turn leads to increased probability of CKD. The direct effect of diabetes duration on CKD is not significant, whereas the indirect effect of diabetes duration on CKD (through hypertension) is once again significant. Model C has a better fit than model A, thus suggesting a more plausible representation of these relationships than model A. The close fit of model D (compared with model C) assessing the role of diabetes leading to periodontal disease suggests that CKD has a significant direct effect on periodontal disease. Diabetes duration seems to have an impact on periodontal disease, both directly and indirectly through increased probability of hypertension and CKD.

In summary, models A, C, and D seem to be the most plausible models. Each model suggests that a bidirectional

relationship may exist between CKD and periodontal disease. Periodontal disease impacts CKD directly, CKD impacts periodontal disease directly, and periodontal disease indirectly affects CKD through diabetes duration and hypertension. Results from models A, C, and D also suggest a bidirectional relationship between periodontal disease and diabetes duration. These findings support a direct relationship of diabetes with CKD (model D) and that diabetes impacts CKD indirectly through periodontal disease (model B) and hypertension.

DISCUSSION

This US population-based study investigated a possible bidirectional relationship between CKD and periodontal disease. We began with multivariable logistic regression models to examine the independent association between CKD and periodontal disease, and used the results of these inquiries to test for mediation and to design structural equation models to determine direct and indirect relationships of periodontal disease and CKD, and vice versa.

It has been shown that diabetes is associated with periodontal disease in a bidirectional relationship. Whether periodontal disease has a causal relationship with diabetes has yet to be determined, as the findings have been equivocal.[24]

We took great care to design multivariable logistic regression models that would control for the potential risk factors for CKD, and to investigate the role diabetes among the other 14 variables. Although model 1 unexpectedly found diabetes glycemic control was not associated with CKD when considering 14 other potential risk factors, when only five other variables recently reported[23] were considered in model 2, diabetes glycemic control was associated with CKD. To further separate out the effects of diabetes on CKD while simultaneously taking into account the other 13 variables in model 3 (without periodontal disease), this allowed us to determine diabetes duration was independently associated with CKD, and provided a stepping stone to model 4. When periodontal disease score was added in model 4, periodontal disease was significantly associated with CKD.

Models 1 and 4 indicate the robustness of the effect of periodontal status on CKD, as periodontal status was independently associated with CKD irrespective of periodontal status definition. The effect of periodontal disease was further substantiated by model 4, because when periodontal disease score was added to model 3, there was a 25% decrease in the effect of the strongest risk factor, namely older age. Using these four models allowed us to demonstrate the importance of simultaneously taking into account other potential risk factors, and the importance of the definitions used for the variables. Furthermore, the periodontal disease and CKD relationship was found to be mediated by diabetes duration and hypertension. Our results suggest that the effect of periodontal disease on CKD may have two components, a direct effect and an effect mediated by diabetes duration and hypertension.

We next designed several biologically plausible structural equation models to determine whether there is either a direct or indirect effect of periodontal disease on CKD. The structural equation models were derived in large part using the multivariable logistic regression models reported herein. This approach allows a variable to function as both an independent and dependent variable,[25] hence permitting tests of the bidirectional association between CKD and periodontal disease. We were now able to demonstrate a bidirectional relationship between periodontal disease and CKD, as well as mediation of the effect via diabetes duration and hypertension.

We acknowledge that causal inference is generally not possible with cross-sectional data because of the inability to assess temporal association. Therefore, structural equation modeling was performed because it allowed us to test whether hypothesised causal relationships were statistically plausible. The structural equation models were found to have a close fit, suggesting that the proposed causal relationships can be considered plausible, given the potentially complex relationships between CKD and periodontal disease,[26] and paths can be tested for significance. Longitudinal studies are necessary to further examine the nature of this possible bidirectional relationship.

These results open up exciting new avenues of investigation. How might periodontal disease impact CKD and vice versa? Chronic inflammation is a risk factor for both atherosclerotic cardiovascular disease and CKD. Evidence supports the notion that chronic inflammation contributes to the pathogenesis of hypertension and diabetes, both major risk factors for cardiovascular disease and CKD.[27] It is biologically plausible to hypothesise that periodontal disease, a source of systemic inflammatory burden, is a risk factor for CKD.[7–11] CKD is an immunocompromised state characterised by impaired function of T- and B-cells as well as monocyte/macrophages.[28,29] Patients with CKD have increased risk of infection because of the decreased immune response seen in the uremic milieu.[30] Thus, CKD may predispose to the chronic infection of periodontal disease, a scenario that should be explored in future studies. Inflammation may be an important link between CKD and periodontal disease,[26] a possibility that warrants further testing of the bidirectional relationship, especially in longitudinal studies.

Limitations to this study include inability to infer causality using cross-sectional data. In addition, the method of Baron and Kenny assumes a unidirectional relationship between CKD and periodontal disease. This limitation was addressed through the more powerful structural equation modeling approach which allows a variable to function as both an independent and dependent variable,[31] permitting tests of the bidirectional association between CKD and periodontal disease.

It is not merely the unique application of sophisticated statistical methodology that gives this report its importance. The data described herein suggest potential pathways to early prevention and detection of CKD via screening and treatment of periodontal disease. The significance of these

data is further underscored by the recent consensus paper on the periodontal–cardiovascular disease connection.[32] This consensus statement recommends that periodontists inform patients with periodontal disease that they may have increased risk for cardiovascular disease. Recommendations were based on evidence from multiple studies supporting the role of periodontal disease in increased systemic inflammation. It is this inflammatory component of periodontal disease that is also relevant to CKD. Nephrologists and other physicians currently advise adult patients to reduce risk for CKD by modifying behavior (for example, smoking cessation, diet modification, exercise) and compliance with medical therapy such as antihypertensive medications.[1,33–35] The possibility that oral hygiene and periodontal therapy may have a place in prevention of CKD, while intriguing, remains to be determined in future intervention studies.

Our study has several strengths. Diabetes was found to be associated with CKD based on an analytical approach that assessed the same factors in a recently published model,[23] and in a separate model that incorporated eight additional potential risk factors. The relationship between CKD, diabetes, and periodontal disease was investigated further using the Baron and Kenny mediation approach,[36] which found diabetes duration and hypertension were mediators in the relationship between CKD and periodontal disease. Our structural equation models investigated direct and indirect effects in the assessment of four path models, the results of which support this first report of a bidirectional relationship between CKD and periodontal disease with mediation by diabetes duration and hypertension. Furthermore, Third National Health and Nutrition Examination Survey, 1988–1994 (NHANES III) sampling methodology is designed to represent the US population and questionnaire, examination and laboratory data were collected in an unbiased manner, such that the participants were unaware of this study of CKD. Finally, data collection was not restricted to only adults who visited health care providers.

This is the first report in which sophisticated statistical methodology is applied to the study of periodontal disease, CKD, and multiple other factors. Though it will probably not surprise clinicians that periodontal disease is associated with CKD and vice versa, it is nonetheless important to substantiate repeated clinical impressions using robust statistical methods such as this. It is also important to verify that an apparent association, for example, between periodontal disease and CKD, is an independent relationship that is not actually an association between some other factor such as socioeconomic status or older age. The disciplines of epidemiology and statistics provide powerful tools to do just that. This report is an important step in understanding the relationship between periodontal disease and CKD. It is especially crucial to understand the impact of periodontal disease on CKD in that periodontal disease can be effectively treated or better yet prevented. CKD has a devastating impact on the individual's quality and length of life, whereas its burden to the health care system and the US economy is nothing short of staggering. Lessening the impact of CKD using the simple techniques and inexpensive materials that will prevent periodontal disease would be a great accomplishment.

In summary, we used structural equation modeling methodology to allow for simultaneous modeling of direct and indirect effects in testing the bidirectional relationship between CKD and periodontal disease. To the authors' knowledge, the structural equation models in Figure 1 with CKD leading to periodontal disease have not been previously explored in the literature. Collectively, these findings support the conclusion that periodontal disease is independently associated with CKD in a bidirectional relationship that is mediated by diabetes duration and hypertension in US adults. Additional prospective as well as interventional studies of the bidirectional relationship between CKD and periodontal disease are needed to accumulate empirical data to test causal inference and to assess the possible reduction in incidence, progression, and complications of CKD that periodontal care may provide. Further substantive and methodological research is needed to assess the contribution of these factors when estimating risk for CKD or periodontal disease.

MATERIALS AND METHODS

Study population

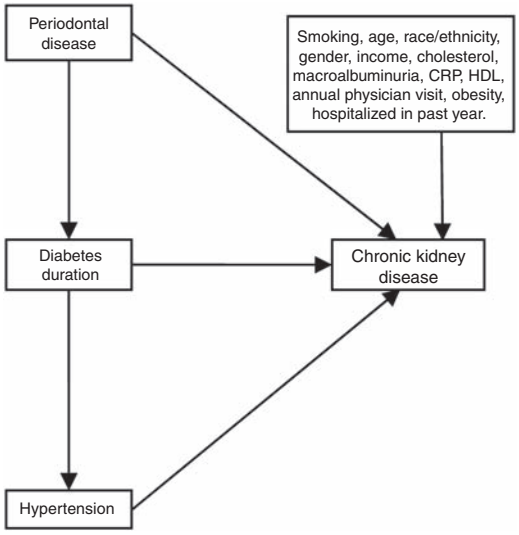
This cross-sectional study used the NHANES III, a public-use data set of civilian, non-institutionalised individuals that is representative of the US population.[37] The University of Kansas School of Medicine–Wichita institutional review board determined this study was not human subject research because it involved the use of de-identified data and did not involve the collection of data concerning human subjects. All investigators complied with the Data Use Restrictions. This study assessed 11,211 adults 18 years of age and older, representing 118.2 million Americans, with information on kidney function, periodontal status, and the other factors tested in the multivariable modeling.

Description of main outcome

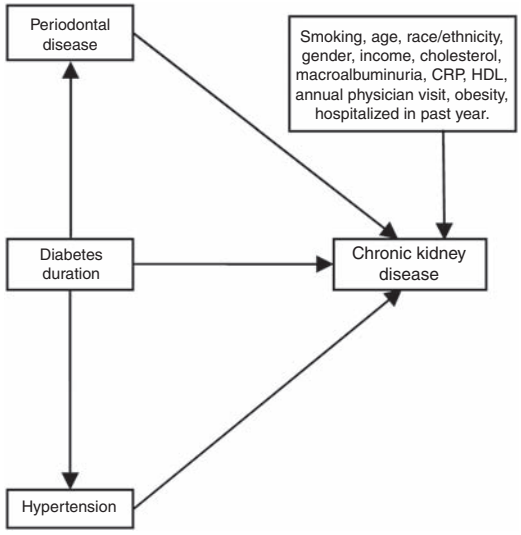
The main outcome was the presence or absence of moderate-to-severe CKD defined as an estimated glomerular filtration rate of 15–59 ml/min per 1.73 m^2.[1] The estimated glomerular filtration rate was calculated using the simplified Modification of Diet in Renal Disease Study equation: glomerular filtration rate $= 186.3 \times$ (serum creatinine in mg/dl)$^{-1.154} \times$ age$^{-0.203} \times$ (0.742 if female) $\times$ (1.21 if non-Hispanic black). The serum creatinine value was calibrated by subtracting the value of 0.23 mg/dl to align the NHANES measures with creatinine assays in the aforementioned equation.[38]

Description of main exposure and potential risk factors

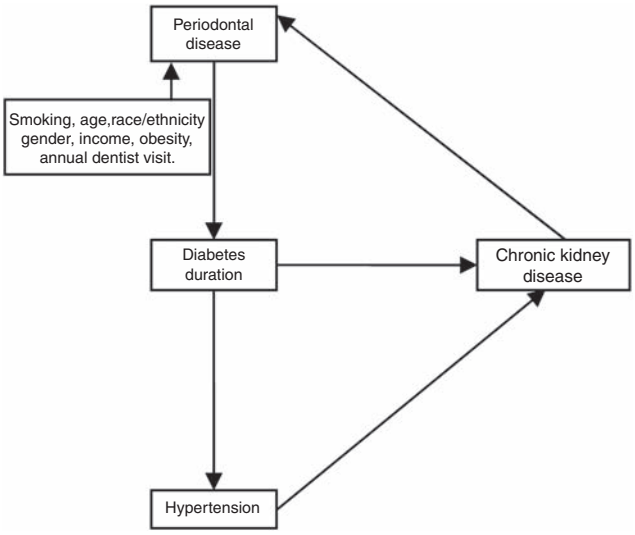
The main exposure was periodontal status assessed by clinical examination performed by a dentist on all participants who consented, and categorised as no periodontal disease, periodontal disease, or edentulous (that is, no natural teeth). Periodontal disease was defined as one or more sites with both $\geqslant 4$ mm loss of attachment and bleeding on the same tooth.[39] In addition, we developed a novel periodontal disease score to address both partial and complete tooth loss. This score was derived by multiplying the proportion of teeth classified as having periodontal disease by 100.



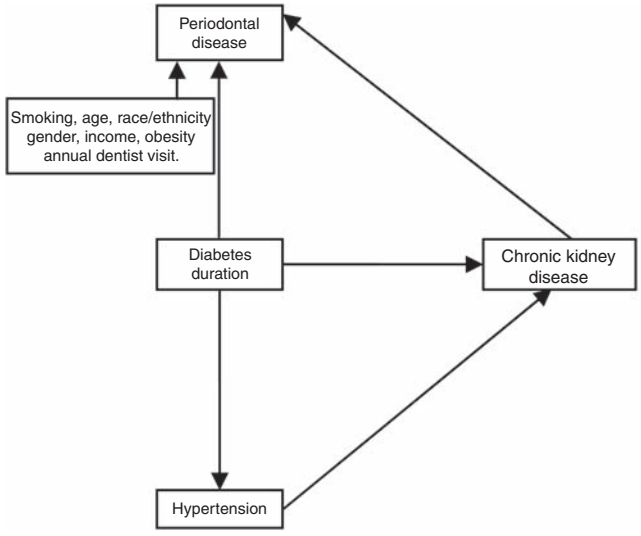
Model A. Chronic kidney disease structural equation model



Model B. Chronic kidney disease structural equation model



Model C. Periodontal disease structural equation model



Model D. Periodontal disease structural equation model

Figure 1 | Hypothetical structural equation models outlining four possible relationships between CKD and periodontal disease. Not shown are relevant potential risk factors of diabetes, for example, obesity, hypertension, and race/ethnicity. Abbreviations: CKD, chronic kidney disease; CRP, C-reactive protein, HDL, high-density lipoprotein.

A value of zero was assigned if the tooth was present and periodontal disease was absent, a value of 1 was assigned if the tooth was present and periodontal disease was present, or a value of 0.72 was assigned if the tooth was absent, assuming that 72% of missing teeth were extracted because of the periodontal disease.[40] The proportion is the sum of the periodontal disease status values for all the teeth present and missing divided by 14, which is the total number of teeth evaluated for each individual in NHANES III.

The other potential risk factors including socioeconomic status, health status, health behavior and biomarkers, anthropometric assessment, and health care utilisation are depicted in the descriptive summary in Table 2.

Statistical analyses

Multivariable logistic regression modeling. Multivariable logistic regression models were fitted to test the hypothesis that periodontal disease was independently associated with CKD. Estimates of OR_{Adj}, and 95% CI describe the independent effects of the potential risk factors. This analytic approach used design-based logistic regression modeling in SUDAAN, version 10 (Research Triangle Institute, Research Triangle Park, NC) to estimate the direct relationships of periodontal status (main exposure) and other scientifically relevant risk factors with the odds of having CKD (main outcome), taking the complex design features and sampling weights of the NHANES III into account. (Multivariable logistic regression models are designated numerically to distinguish them from the structural equation models that are designated alphabetically below.) Previous work motivated the report herein of the following four models:

(1) Model 1: A full model with all 15 potential risk factors, including the addition of diabetes status, BMI, and CRP to Fisher *et al.*[9]
(2) Model 2: Coresh *et al.*[23] with six potential risk factors.

Table 2 | Descriptive summary of characteristics of study population[a]

Socioeconomic status	
Mean age (continuous)	41.6 (s.e.:0.47)
Older age	
Yes: ⩾60 years old	17.4%
No: 18–59 years old	82.6%
Race/ethnicity	
Non-Hispanic white	82.2%
Non-Hispanic black	11.5%
Mexican–American	6.3%
Gender	
Female	52.4%
Male	47.6%
Lower income	
Yes: <$20,000 annual household income	31.2%
No: ⩾$20,000 annual household income	68.8%
Health status	
Chronic kidney disease	
Yes: 15–59 ml per min per 1.73 m^2	3.3%
No: ⩾60 ml per min per 1.73 m^2	96.7%
Periodontal disease	
Edentulous	10.3%
Periodontal disease (⩾1 site with both ⩾4 mm loss of attachment and bleeding on the same tooth)	5.5%
No periodontal disease	84.2%
Diabetes status[b]	
Diabetes with poor control (⩾7% glycated hemoglobin)	2.4%
Diabetes with good control (<7% glycated hemoglobin)	2.0%
No diabetes	95.6%
Mean diabetes duration (years)	0.40 (s.e.:0.03)
Hypertension	
Yes: >140 mm Hg systolic pressure, or >90 mm Hg diastolic pressure, or told on two or more different visits that one had hypertension	22.5%
No: ⩽140 mm Hg systolic pressure, and ⩽90 mm Hg diastolic pressure, and not told on two or more different visits that one had hypertension	77.5%
Health behavior and biomarkers	
Smoking	
Never smoker	46.9%
Former smoker	22.5%
Current smoker	30.6%
Macroalbuminuria	
Yes: ⩾300 mg/g urinary albumin-to-creatinine excretion ratio	0.8%
No: <300 mg/g urinary albumin-to-creatinine excretion ratio	99.2%
Mean CRP (continuous)	0.39 (s.e.: 0.01)
High total cholesterol	
Yes: ⩾240 mg/dl total serum cholesterol	16.9%
No: <240 mg/dl total serum cholesterol	83.1%
Low HDL	
Yes: ⩽35 mg/dl	12.5%
No: >35 mg/dl	87.5%
Anthropometric assessment	
Mean BMI (continuous)	26.27 (s.e.:0.11)
Health care utilization	
Annual physician visit	
Yes	80.7%
No	19.3%
Hospitalizations in past year	
Yes	11.1%
No	88.9%

Abbreviations: BMI, body mass index; CRP, C-reactive protein; HDL, high-density lipoprotein.
[a]Excluding those who reported former or never smoking but were current smokers based on serum cotinine levels ⩾15 ng/ml.[41]
[b]Diabetes was defined as fasting plasma glucose ⩾126 mg/dl or plasma glucose ⩾200 mg/dl after an oral glucose tolerance test or self-reported diagnosis of diabetes by a physician.
Note: weighted percent for *N*=11,211 adults with data for all variables.

(3) Model 3: A full model with all 14 potential risk factors, including the addition of diabetes duration to Fisher *et al.*,[9] except for periodontal status.
(4) Model 4: Model 3 with all 15 potential risk factors, including periodontal disease score.

Given the importance of diabetes and hypertension as risk factors for CKD and the potential that the CKD and periodontal disease relationship may be bidirectional, we next used a two-step analytic approach involving (1) tests for mediation, per Baron and Kenny,[36] and (2) a structural equation modeling approach[25] to examine the more complex direct and indirect effects of periodontal disease on CKD, and vice versa. Figure 1 provides the basic theoretical forms of the structural equation models tested.

Examination of diabetes and hypertension as possible mediators of the relationship between CKD and periodontal disease. The Baron and Kenny approach[36] is an analytical method that assesses the mediation of an effect by a factor/variable. Using this approach, a model without the potential mediator is compared with the same model except with the potential mediator to determine if an observed effect is mediated by a particular variable. This would be indicated by the exposure or potential risk factor predicting the mediator and the mediator predicting the outcome. First, diabetes was examined as a potential mediator of the relationship between CKD and periodontal disease.[9] A logistic regression model was fitted for duration of diabetes as a function of periodontal disease and other potential risk factors in the final model of CKD depicted in Figure 1. Given that periodontal disease had already been shown to be associated with CKD,[9] a third model was fitted that added diabetes duration to the CKD–periodontal disease model to determine if the relationship remained after adding diabetes duration. Next, hypertension was examined as a possible mediator of the relationship between CKD and periodontal disease using a similar methodology as described to assess diabetes.

Structural equation models. Whereas the logistic regression method only considers the direct effect of periodontal disease on CKD when controlling for the direct effects of the other potential risk factors, structural equation models assesses both the direct and indirect effects of diabetes duration, hypertension, and periodontal disease on CKD. The Mplus software (Version 5; http://www.statmodel.com)

was used to fit the structural equation models depicted in Figure 1. This software has the unique ability to fit complex path models to both continuous and categorical variables, whereas also taking complex sample design features into account when computing estimates of path coefficients, standard errors, and tests of overall model fit.[31] Measures of overall model fit (that is, general design-based χ^2-test of goodness of fit) produced by Mplus[31] were evaluated to determine whether the four hypothesised path models were plausible. Individual path coefficients in the model were tested for statistical significance given an acceptable fit of each model, and direct, indirect and total effects of each variable on CKD and periodontal disease were interpreted as a part of the hypothesis-generating analysis. The following structural equation models were fitted:

(1) Model A for CKD outcome: Periodontal disease, diabetes duration, and hypertension leading to CKD, with periodontal disease leading to diabetes, simultaneously adjusting for 12 other potential risk factors.
(2) Model B for CKD outcome: Periodontal disease, diabetes duration, and hypertension leading to CKD, with diabetes leading to periodontal disease, simultaneously adjusting for 12 other potential risk factors.
(3) Model C for periodontal disease outcome: CKD leading to periodontal disease, with diabetes duration and hypertension leading to CKD, simultaneously adjusting for seven other potential risk factors.
(4) Model D for periodontal disease outcome: CKD and diabetes duration leading to periodontal disease, with diabetes duration and hypertension leading to CKD.

DISCLOSURE

All the authors declared no competing interests.

ACKNOWLEDGMENTS

This study was supported by the NIH DE016031.

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at http://www.nature.com/ki

REFERENCES

1. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002; **39**(2 Suppl 1): S1–S266.
2. Centers for Disease Control and Prevention. Prevalence of chronic kidney disease and associated risk factors – United States, 1999–2004. *MMWR Morb Mortal Wkly Rep* 2007; **56**: 161–165.
3. Coresh J, Byrd-Hold D, Astor BC *et al.* Chronic kidney disease awareness, prevalence, and trends among US adults, 1999 to 2000. *J Am Soc Nephrol* 2005; **16**: 180–188.
4. Go A, Chertow G, Fan D *et al.* Chronic kidney disease and the risks of death, cardiovascular events and hospitalization. *N Engl J Med* 2004; **351**: 1296–1305.
5. Keith DS, Nichols GA, Gullion CM *et al.* Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. *Arch Intern Med* 2004; **164**: 659–663.
6. Rahman M, Pressel S, Davis BR *et al.* Cardiovascular outcomes in high-risk hypertensive patients stratified by baseline glomerular filtration rate. *Ann Intern Med* 2006; **144**: 172–180.
7. Fisher MA, Taylor GW. A prediction model for chronic kidney disease includes periodontal disease. *J Periodontol* 2009; **80**: 16–23.
8. Fisher MA, Taylor GW, Papapanou PN *et al.* Clinical and serological markers of periodontal infection and chronic kidney disease. *J Periodontol* 2008; **79**: 1670–1678.
9. Fisher MA, Taylor GW, Shelton BJ *et al.* Periodontal disease and other non-traditional risk factors for CKD. *Am J Kidney Dis* 2008; **51**: 45–52.
10. Bang H, Vupputuri S, Shoham DA *et al.* Screening for occult renal disease (SCORED): a simple prediction model for chronic kidney disease. *Arch Intern Med* 2007; **167**: 374–381.
11. Kshirsagar AV, Moss KL, Elter JR *et al.* Periodontal disease is associated with renal insufficiency in the Atherosclerosis Risk in Communities (ARIC) study. *Am J Kidney Dis* 2005; **45**: 650–657.
12. Kshirsagar AV, Craig RG, Moss KL *et al.* Periodontal disease adversely affects the survival of patients with end-stage renal disease. *Kidney Int* 2009; **75**: 746–751.
13. Dye BA, Choudhary K, Shea S *et al.* Serum antibodies to periodontal pathogens and markers of systemic inflammation. *J Clin Periodontol* 2005; **32**: 1189–1199.
14. Cazzavillan S, Ratanarat R, Segala C *et al.* Inflammation and subclinical infection in chronic kidney disease: a molecular approach. *Blood Purif* 2007; **25**: 69–76.
15. Stenvinkel P. New insights on inflammation in chronic kidney disease-genetic and non-genetic factors. *Nephrol Ther* 2006; **2**: 111–119.
16. Phipps KR, Stevens VJ. Relative contribution of caries and periodontal disease in adult tooth loss for an HMO dental population. *J Pub Hlth Dent* 1995; **55**: 250–252.
17. Loos BG. Systemic markers of Inflammation in periodontitis. *J Periodontol* 2005; **76**(11 Suppl): 2106–2115.
18. Offenbacher S, Beck JD. A perspective on the potential cardio-protective benefits of periodontal therapy. *Am Heart J* 2005; **149**: 950–954.
19. Slade GD, Ghezzi EM, Heiss G *et al.* Relationship between periodontal disease and C-reactive protein among adults in the Atherosclerosis Risk in Communities study. *Arch Intern Med* 2003; **163**: 1172–1179.
20. Slade GD, Offenbacher S, Beck JD *et al.* Acute-phase inflammatory response to periodontal disease in the US population. *J Dent Res* 2000; **79**: 49–57.
21. Beck JD, Offenbacher S. The association between periodontal diseases and cardiovascular diseases: a state-of-the-science review. *Ann Periodontol* 2001; **6**: 9–15.
22. Teng YT, Taylor GW, Scannapieco F *et al.* Periodontal health and systemic disorders. *J Can Dent Assoc* 2002; **68**: 188–192.
23. Coresh J, Selvin E, Stevens LA *et al.* Prevalence of chronic kidney disease in the United States. *JAMA* 2007; **298**: 2038–2047.
24. Taylor GW, Borgnakke WS. Periodontal disease: associations with diabetes, glycemic control and complications. *Oral Dis* 2008; **14**: 191–203.
25. Kline RB. *Principles and Practice of Structural Equation Modeling*. 2nd edn, The Guilford Press: New York, 2005.
26. Fisher MA, Borgnakke WS, Taylor GW. Periodontal disease as a risk marker in coronary heart disease and chronic kidney disease. *Curr Opin Nephrol Hypertens* 2010; in press.
27. Tonelli M, Pfeffer MA. Kidney disease and cardiovascular risk. *Ann Rev Med* 2007; **58**: 123–139.
28. Chatenoud L, Herbelin A, Beaurain G *et al.* Immune deficiency of the uremic patient. *Adv Nephrol Necker Hosp* 1990; **19**: 259–274.
29. Girndt M, Sester M, Sester U *et al.* Molecular aspects of T- and B-cell function in uremia. *Kidney Int Suppl* 2001; **78**: S206–S211.
30. Johnson D, Fleming S. The use of vaccines in renal failure. *Clin Pharmacokinet* 1992; **22**: 434–446.
31. Mplus Manual, Mplus Technical Appendix 1, www.statmodel.com.
32. Friedewald VE, Kornman KS, Beck JD *et al.* The American Journal of Cardiology and Journal of Periodontology editors' consensus: periodontitis and atherosclerotic cardiovascular disease. *J Periodontol* 2009; **80**: 1021–1032.
33. US Department of Health and Human Services. *The Health Benefits of Smoking Cessation: A Report of the Surgeon General*. US Department of Health and Human Services, CDC: Rockville, MD, 1990.
34. Jamerson KA. Preventing chronic kidney disease in special populations. *Am J Hypertens* 2005; **18**(4 Pt 2): 106S–111S.
35. Rahman M, Pressel S, Davis BR *et al.* Renal outcomes in high-risk hypertensive patients treated with an angiotensin-converting enzyme inhibitor or a calcium channel blocker vs a diuretic. *Arch Intern Med* 2005; **165**: 936–946.
36. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J Pers Soc Psychol* 1986; **51**: 1173–1182.

37. National Center for Health Statistics. National Health and Nutrition Examination Survey III Documentation, Codebook, and Data Files. (available http://www.cdc.gov/nchs/about/major/nhanes/datalink.htm#NHANESIII).
38. Coresh J, Astor BC, McQuillan G *et al.* Calibration and random variation of the serum creatinine assay as critical elements of using equations to estimate glomerular filtration rate. *Am J Kidney Dis* 2002; **39**: 920–929.
39. Fisher MA, Taylor GW, Tilashalski KR. Smokeless tobacco and severe active periodontal disease, NHANES III. *J Dent Res* 2005; **84**: 705–710.
40. Shlossman M, Knowler WC, Pettitt DJ *et al.* Type 2 diabetes mellitus and periodontal disease. *J Am Dent Assoc* 1990; **121**: 532–536.
41. Pirkle JL, Flegal KM, Bernert JT *et al.* Exposure of the US population to environmental tobacco smoke. *JAMA* 1996; **275**: 1233–1240.